

Heteroaryl diazacycloalkanes, their preparation and use;

The present invention relates to novel heteroaryl diazacycloalkane derivatives which are cholinergic ligands at nicotinic ACh receptors. The compounds of the invention are useful for the treatment of conditions or disorders or diseases involving the cholinergic system of the central or peripheral nervous system, dementia, pain, inflammatory diseases, diseases caused by smooth muscle contractions and as assistance in the cessation of chemical substance abuse.

Background

The endogenous cholinergic neurotransmitter, acetylcholine, exert its biological effect via two types of cholinergic receptors; the muscarinic ACh receptors and the nicotinic ACh receptors. As it is well established that muscarinic ACh receptors dominate quantitatively over nicotinic ACh receptors in the brain area important to memory and cognition, much research aimed at the development of agents for the treatment of memory related disorders have focused on the synthesis of muscarinic ACh receptor modulators. Recently, however, an interest in the development of nicotinic ACh receptor modulators has emerged. Several diseases are associated with degeneration of the cholinergic system i.e. senile dementia of the Alzheimer type, vascular dementia and cognitive impairment due to the organic brain damage disease related directly to alcoholism. Indeed several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency or a serotonergic deficiency. Alzheimer's disease is characterised by a profound loss of memory and cognitive functions caused by a severe depletion of cholinergic neurons, i.e. neurons that release acetylcholine. A reduction in the number of nicotinic ACh receptors are also observed with the progression of Alzheimer's disease. It is believed that the neurons in the cortex that die with the progression of Alzheimer's disease do so because of lack of stimulation of the nicotinic ACh receptors. It is predicted that treatment of Alzheimer's patients with nicotinic ACh receptor modulators will not only improve the memory of patients but in addition act to keep these neurons alive. Smoking actually seems to protect individuals against neurodegeneration and compounds behaving on these receptor may very likely have a generally neuroprotective effect.

However degeneration of the cholinergic system is not limited to individuals suffering from i.e. Alzheimers disease but is also seen in healthy aged adults and rats. Therefore it is suggested that the cholinergic system is involved and partly responsible for the memory disturbances

seen in aged animals and humans. Nicotine receptor modulator may therefore be useful in the treatment of Alzheimer's disease, memory loss, memory dysfunction, AIDS-dementia, senile dementia or neurodegenerative disorders.

Parkinsons disease appears to involve degeneration of dopaminergic neurons. One symptom
5 of the disease has been observed to be loss of nicotinic receptors associated with the dopaminergic neurons and possibly interfering with the process of release of dopamine. As sustained nicotine administration increases the number of receptors present, administration of nicotine receptor modulators may ameliorate the symptoms of Parkinson's disease. Other condition or disorders or disease ascribed to deficiencies in the dopaminergic system is: drug
10 addiction, depression, obesity and narcolepsy.

Tourette's syndrome is a neuropsychiatric disorder involving a range of neurological and behavioral symptoms. It is believed that neurotransmitter dysfunction is involved though the pathophysiology is still unknown and that nicotine will be beneficial in the treatment of the disease (Devor et. al. The Lancet, vol. 8670 p. 1046, 1989)

15 Schizophrenia is a severe psychiatric illness. Neuroleptic compounds has been used in the treatment of the disease, the effect of the compounds is believed to be interaction in the dopaminergic system. Nicotine is proposed to be effective in the treatment of schizophrenia (ie. Adler et. al. Biol. Psychiatry, Vol. 32, p. 607-616, 1992.)

Nicotine has been reported to have en effect on neurotransmitter release in several systems.
20 Release of acetylcholine and dopamine by neurons upon administration of nicotine has been reported and release of norepinephrine by Hall et. al. (Biochem. Pharmacol. vol. 21, 1829-1838, 1972) Release of serotonin by Hery et. al. (Arch. Int. Pharmacodyn. Ther. vol. 296. p. 91-97, 1977). Release of glutamate by Toth et. al (Neurochem. Res. vol. 17, p. 265-271, 1992)

25 The serotonin system and dysfunction's of the serotonergic system is believed to be involved in diseases or conditions or disorders like: anxiety, depression, eating disorders, obsessive compulsive disorder, panic disorders, chemical substance abuse, alcoholism, pain, memory deficits and anxiety, pseudodementia, Ganser's syndrome, migraine pain, bulimia, obesity, pre-menstrual syndrome or late luteal phase syndrome, tobacco abuse, post-traumatic
30 syndrome, social phobia, chronic fatigue syndrome, premature ejaculation, erectile difficulty, anorexia nervosa, disorders of sleep, autism, mutism or trichotillomania.

Nicotine improves concentration and task performance. Therefore compounds exhibiting nicotine receptor modulating properties will be likely to be useful compounds in the treatment of learning deficit, cognition deficit, attention deficit, attention deficit hyperactivity disorder and
35 dyslexia.

Tobacco use and especially cigarette smoking is recognised as a serious health problem. However nicotine withdrawal symptoms associated with smoking cessation makes it difficult to break this habit. Withdrawal symptoms include anger, anxiety, difficulties in concentrating, restlessness, decreased heart rate and increased appetite and weight gain. Nicotine itself has
5 shown to ease the withdrawal symptoms.

Withdrawal from addictive substances, i.e. opiates, benzodiazepines, ethanol, tobacco or nicotine, is in general a traumatic experience characterised by anxiety and frustration.

Nicotine has been found to be effective in reducing anger, irritability, frustration and feelings
10 of tension without causing general response depression, drowsiness or sedation and compounds having same characteristics as nicotine is likely to have same effects.

Mild to moderate pain is normally treatable with NSAID's (non-steroidal anti-inflammatory drugs) while opiates are used preferentially for moderate to severe pain. The opiates have
15 some well-known side-effects, including chemical dependence and abuse potential as well as a depressive effect on the respiratory and gastrointestinal system. There exists therefore a strong need for analgesic compounds that do not exhibit these side effects and which can relieve mild, moderate and severe pain of acute, chronic or recurrent character as well as migraine pain and postoperative pain, phantom limb pain.

Epibatidine, a compound isolated from the skin of a poison frog, is a very potent analgesic with an approximate potency of 500 times that of morphine. The analgesic effect is not affected by naloxone, which is an indication of a negligible affinity for the opiate receptors. Epibatidine is a nicotinic cholinergic receptor agonist and it is therefore very likely, that compounds possessing this receptor modulating character will also show a strong analgesic
25 response.

The compounds of the present invention has proven useful for modulation of smooth muscle contractions and may therefore be used in the treatment or prevention of condition or disorders or diseases inherent from smooth muscle contractions like i.e. convulsive disorders, angina pectoris, premature labor, convulsions, diarrhoea, asthma, epilepsy, tardive
30 dyskinesia, hyperkinesia.

Further, it is well known that nicotine has an effect on appetite and it is predicted that modulators at the nicotine ACh receptor may be useful as appetite suppressants in the treatment of obesity and eating disorders.

The cholinergic receptors play an important role in the functioning of muscles, organs and generally in the central or peripheral system. There are also complex interactions between cholinergic receptors and the function of receptors of other neurotransmitters such as dopamine, serotonin and noradrenaline.

- 5 It is likely that nicotine receptor modulator compounds can be effective in preventing or treating conditions or disorders or diseases like: inflammation, inflammatory skin conditions, Chron's disease, inflammatory bowel disease, irritable colon, ulcerative colitis, irritable colon, diarrhoea, neurodegeneration, peripheral neuropathy, amyotrophic lateral sclerosis, nociception, endocrine disorders, thyrotoxicosis, pheochromocytoma, hypertension, 10 arrhythmias, mania, manic depression, Huntington's disease, jetlag.

The compounds of the present invention are nicotine receptor modulators and has the potential to exhibit nicotinic pharmacology, preferentially without the side effects associated with nicotine itself. Additionally, the compounds are expected to have the potential as 15 enhancers of neurotransmitter secretion and suppress symptoms associated with a low activity of neurotransmitters.

Objects of the Invention

- 20 It is an object of the present invention to provide novel heteroaryl diazacycloalkane derivatives which are useful for the treatment of a range of diseases and disorders characterized by decreased or elevated cholinergic function or responsive to the activity of nicotinic ACh receptor modulators.
- 25 Another object of the present invention is to provide novel pharmaceutical compositions containing these compounds, as well as methods for the preparation thereof and methods for the treatment therewith.

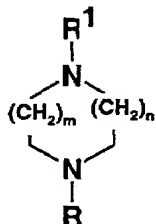
Another object of the present invention is to provide a method of treatment of diseases and 30 disorders responsive to the activity of nicotinic Ach receptor modulators.

Other objects will become apparent hereinafter to one skilled in the art.

Summary of the Invention

The invention then, inter alia, comprises the following, alone or in combination:

A compound represented by the general formula



(I)

any of its enantiomers or any mixture thereof, isotopes thereof or a pharmaceutically acceptable salt thereof;

10 wherein

n is 1, 2 or 3;

m is 0, 1 or 2;

R represents hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aralkyl, alkoxy, alkenoxy, alkenoxy, alkenoxy, thioalkenyl, thioalkynyl, ,

15

or with the proviso that R^1 and R are equal then R is

a monocyclic 5 to 6 membered heterocyclic group which may be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, thioalkenyl, thioalkynyl, , selenoalkyl, selenoalkenyl, selenoalkynyl, methylenedioxy, halogen, CF_3 , OCF_3 , CN, amino, nitro, $-COOR^3$, $-CONR^2R^3$, $-NH-CO_2R^2$, $NHCO-R^2$, $-OCO-NR^2R^3$; wherein R^2 and R^3 independently represents hydrogen or alkyl;

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R^1 represents

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a monocyclic 5 to 6 membered heterocyclic group which may be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, cycloalkoxyalkoxy, alkenoxy, alkynoxy, thioalkenyl, thioalkynyl, , selenoalkyl, selenoalkenyl, selenoalkynyl, methylenedioxy, halogen, CF_3 , OCF_3 , CN, amino, nitro, $-COOR^3$, $-CONR^2R^3$, $-NH-CO_2R^2$, $NHCO-R^2$, $-OCO-NR^2R^3$;

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wherein R^2 and R^3 independently represents hydrogen or alkyl;

aryl optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, CF₃, OCF₃, CN, amino and nitro;

-X-alkyl-Y-alkyl wherein X and Y independently represents O, S, NH, N-alkyl or Se; and alkyl is optionally substituted with alkoxy, epoxy or thioalkoxy;

-X-(alk)_o-aryl wherein o is 0 or 1 and alk represents alkyl, alkenyl or alkynyl and X represents O, S, NH, N-alkyl or Se; aryl is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, CF₃, OCF₃, CN, amino and nitro;

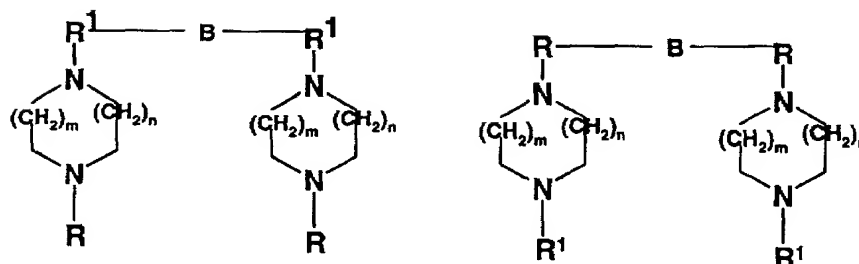
10 -X-(alk)_o-Z wherein o is 0 or 1 and alk represents alkyl, alkenyl or alkynyl and X represents O, S, NH, N-alkyl or Se and Z represents a 5- or 6 - membered monocyclic heterocyclic group; optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, CF₃, OCF₃, CN, amino and nitro;

15 - a monocyclic 5 to 6 membered heterocyclic group optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, CF₃, OCF₃, CN, amino and nitro;

(alk)_o-HET, wherein o is 0 or 1 and alk represents alkyl, alkenyl or alkynyl;

20 or R¹ represents a **bicyclic heterocyclic group**, composed of a 5 to 6 membered monocyclic heterocyclic group fused to a benzene ring, and which may be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, alkoxy-alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, CF₃, OCF₃, CN, amino, nitro, aryl optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, CF₃, OCF₃, CN, amino and nitro; and a monocyclic 5 to 6 membered heterocyclic group optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, CF₃, OCF₃, CN, amino and nitro;

30 Or a compound of the invention is represented by the general formula:



wherein R^1 , R, n and m is defined above and B represents a bridging element of the formula:
alk, alk-O-alk, alk-S-alk; wherein alk represents alkyl, alkenyl, alkynyl;

- 5 A pharmaceutical composition, comprising a therapeutically effective amount of a compound of above, or a pharmaceutically acceptable addition salt thereof, together with at least one pharmaceutically acceptable carrier or diluent.

The use of a compound as above for the manufacture of a medicament for the treatment of a
10 disease of a living animal body, including a human, which disease is responsive to the activity of nicotinic ACh receptor modulators.

A compound as above for use as a medicament for treatment of a disease of a living animal body, including a human, which disease is responsive to the activity of nicotinic Ach receptors
15 modulators;

A method of treating a disease of a living animal body, including a human, which disease is responsive to the activity of nicotinic ACh receptor modulators, comprising the step of administering to such a living animal body, including a human, in need thereof a
20 therapeutically effective amount of a compound as above;

Detailed disclosure of the invention

One preferred aspect of the invention is a compound according to formula (I) wherein

25 n is 1, 2 or 3;

m is 0, 1 or 2;

R represents alkyl, alkenyl, alkynyl, alkoxyphenyl, alkenoxyphenyl;

R^1 represents

a monocyclic 5 to 6 membered heterocyclic group which may be substituted one or more times with substituents selected from the group consisting of cycloalkoxyalkoxy, thioalkenyl, thioalkynyl, selenoalkyl, selenoalkenyl, selenoalkynyl;

-X-alkyl-Y-alkyl wherein X and Y independently represents O, S, NH, N-alkyl or

5 Se; and alkyl is optionally substituted with epoxy;

-X-(alk)_o-aryl wherein o is 0 or 1 and alk represents alkenyl or alkynyl and X represents O, S, NH, N-alkyl or Se; aryl is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, CF₃, OCF₃, CN, amino and nitro;

10 -X-(alk)_o-Z wherein o is 0 or 1 and alk represents alkenyl or alkynyl and X represents O, S, NH, N-alkyl or Se and Z represents a 5- or 6 - membered monocyclic heterocyclic group; optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, CF₃, OCF₃, CN, amino and nitro;

15 (alk)_o-HET, wherein o is 0 or 1 and alk represents alkyl, alkenyl or alkynyl;

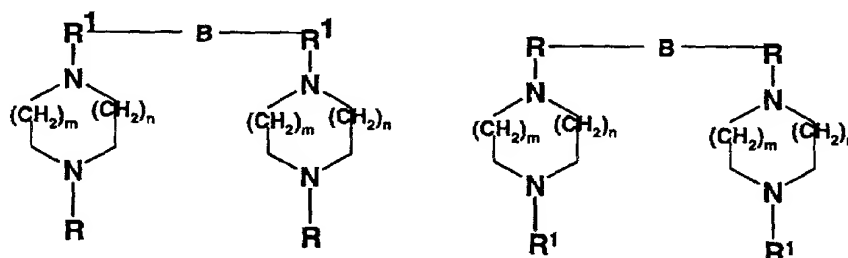
or

with the proviso that R¹ and R are equal then R and R¹ represents:

20 a monocyclic 5 to 6 membered heterocyclic group which may be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, thioalkenyl, thioalkynyl, , selenoalkyl, selenoalkenyl, selenoalkynyl, methylenedioxy, halogen, CF₃, OCF₃, CN, amino, nitro, -COOR³, -CONR²R³, -NH-CO₂R², NHCO-R², -OCO-NR²R³; wherein R² and R³ independently represents hydrogen or alkyl;

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Or a compound of the invention is represented by the general formula:



wherein R¹, R, n and m is defined above and B represents a bridging element of the formula:

alk, alk-O-alk, alk-S-alk; wherein alk represents alkyl, alkenyl, alkynyl;

A preferred aspect of the invention comprises a compound of formula (I) as above wherein the group bridging R and R¹ is a piperazine, a homopiperazine, a 1,4-di-azacyclooctane, a 1,5-di-azacyclooctane, a 1,3-diazacyclohexane or an imidazolidine;

Another preferred aspect of the invention comprises compounds of formula (I) as above wherein R is as defined above and R¹ represents an optionally substituted heteroaryl attached to a piperazine, a homopiperazine, a 1,4-diazacyclooctane, a 1,5-diazacyclooctane, an imidazolidine or a 1,3-diazacyclohexane;

Another preferred aspect of the invention comprises compound of formula (I), as above wherein R¹ represents **isoquinoliny**; or **pyridyl**, **quinoliny**, **pyridaziny** or **pyridiny** all of which may be optionally substituted one or more times with alkoxy, cycloalkoxy, alkoxyalkoxy, alkoxy-epoxy, alkoxyalkenyl, alkoxyalkynyl, alkynyl, alkenyl, thioalkenyl, selenoalkyl, alkoxycycloalkyl, hydroxyalkoxy, thioalkoxy, thioalkylaryl, alkenoxy, alkynoxy, carboxylamido, a bicyclic heterocyclic group, thioalkoxyaryl, thioaryl, hydroxy or trifluoromethanesulfonyloxy; halogen, phenyl optionally substituted with nitro; a monocyclic 5 to 6 membered heterocyclic group optionally substituted with alkyl;

Yet another aspect of the invention comprises a compound of formula (I) as above, wherein R¹ represents

5-(1-heptynyl)-3-pyridyl, 5-(1-hexyny)-3-pyridyl, 5-(1-pentyny)-3-pyridyl, 5-(1-butyly)-3-pyridyl, 5-(1-propyny)-3-pyridyl, 5-ethylenethio-3-pyridyl, 5-(1-propylenethio)-3-pyridyl, 5-(1-butylenethio)-3-pyridyl, 5-(1-pentylenethio)-3-pyridyl, 5-ethyleneseleno-3-pyridyl, 5-(1-propyleneseleno)-3-pyridyl, 5-(1-butyleneseleno)-3-pyridyl, 5-(1-pentyleneseleno)-3-pyridyl, 5-methylseleno-3-pyridyl, 5-ethylseleno-3-pyridyl, 5-propylseleno-3-pyridyl, 5-butylseleno-3-pyridyl, 1-[5-(1-butyl-N-methylamino)-3-pyridyl]

5-(N-azacyclobutenyl)-3-pyridyl, 5-(N-2-pyrrolinyl)-3-pyridine, 5-(N-3-pyrrolinyl)-3-pyridine, 5-N-(1,4,5,6-tetrahydropyridinyl)-3-pyridyl, 5-N-(1,2,5,6-tetrahydropyridinyl)-3-pyridyl, 5-(homopiperazinyl)-3-pyridyl; 5,6-dibromo-3-pyridyl, 5-bromo-6-chloro-3-pyridyl, 6-bromo-5-chloro-3-pyridyl, 6-bromo-3-pyridyl, 5,6-dichloro-3-pyridyl, 6-fluoro-3-pyridyl, 6-iodo-3-pyridyl, 5-chloro-6-fluoro-3-pyridyl, 5-chloro-6-iodo-3-pyridyl, 5-bromo-6-fluoro-3-pyridyl, 5-bromo-6-iodo-3-pyridyl, 6-fluoro-pyridazine, 6-iodopyridazine; 5-pentyloxy-3-pyridyl, 5-(trans-hex-2-en-

1-yloxy)-3-pyridyl, 5-butoxy-3-pyridyl, 5-methoxy-3-pyridyl, 5-propyloxy-3-pyridyl, 5-homopiperazinyl-3-pyridyl, 5-ethoxy-3-pyridyl, 5-propyl-1,2-epoxy-1-oxy-3-pyridyl, 5-phenylacetylenyl-3-pyridyl, 5-(2-ethyl-1-butoxy)-3-pyridyl, 5-(1-methyl-1-prop-2-en-oxy)-3-pyridyl, 5-(cyclobutylmethoxy)-3-pyridyl, 5-(hex-2-en-oxy)-3-pyridyl, 5-(2-methyl-1-prop-1-en-oxy)-3-pyridyl, 5-(1-piperidinyl)-3-pyridyl, 5-(N-azacycloheptyl)-3-pyridyl, 5-(N-azacyclooctanyl)-3-pyridyl, 5-(1-morpholinyl)-3-pyridyl;

A preferred aspect of the invention comprises a compound of formula (I) as above wherein R represents hydrogen, alkyl, alkenyl, or aralkyl; Especially preferred embodiments of the invention are wherein R is hydrogen, methyl, ethyl, propyl, prop-2-en-1-yl;

The most preferred aspect of the invention comprises a compound of formula (I), as above, said compound being:

- 1- [5-1-butyl-N-methylamino)3-pyridyl] homopiperazine
- 5-(1-heptynyl)-3-pyridyl-homopiperazine,
- 5-(1-hexynyl)-3-pyridyl-homopiperazine
- 5-(1-pentynyl)-3-pyridyl-homopiperazine
- 5-(1-butyryl)-3-pyridyl-homopiperazine
- 5-(1-propynyl)-3-pyridyl-homopiperazine
- 5-ethylenethio-3-pyridyl-homopiperazine
- 5-(1-propylenethio)-3-pyridyl-homopiperazine
- 5-(1-butylenethio)-3-pyridyl-homopiperazine
- 5-(1-pentylenethio)-3-pyridyl-homopiperazine
- 5-ethyleneseleno-3-pyridyl-homopiperazine
- 5-(1-propyleneseleno)-3-pyridyl-homopiperazine
- 5-(1-butyleneseleno)-3-pyridyl-homopiperazine
- 5-(1-pentyleneseleno)-3-pyridyl-homopiperazine
- 5-methylseleno-3-pyridyl-homopiperazine
- 5-ethylseleno-3-pyridyl-homopiperazine
- 5-propylseleno-3-pyridyl-homopiperazine
- 5-butylseleno-3-pyridyl-homopiperazine
- 5-(1-azacyclobutene)-3-pyridyl-homopiperazine
- 5-(dihydro-pyrrole)-3-pyridyl-homopiperazine

- 5-(tetrahydropyridine)-3-pyridyl-homopiperazine
- 5-(homopiperazine)-3-pyridyl-homopiperazine
- 5,6-dichloro-3-pyridyl-homopiperazine
- 6-fluoro-3-pyridyl-homopiperazine
- 5 6-iodo-3-pyridyl-homopiperazine
- 5-chloro-6-fluoro-3-pyridyl-homopiperazine
- 5-chloro-6-iodo-3-pyridyl-homopiperazine
- 5-bromo-6-fluoro-3-pyridyl-homopiperazine
- 5-bromo-6-iodo-3-pyridyl-homopiperazine
- 10 6-fluoro-pyridazine-homopiperazine
- 6-iodopyridazine-homopiperazine
- 5-pentyloxy-3-pyridyl-homopiperazine
- 5-pentyloxy-3-pyridyl-piperazine
- 5-(*trans*-hex-2-en-1-yloxy)-3-pyridyl-homopiperazine
- 15 5-(*trans*-hex-2-en-1-yloxy)-3-pyridyl-piperazine
- 5-butoxy-3-pyridyl-1,5-diazacyclooctane
- 5-methoxy-3-pyridyl-4-ethyl-piperazine
- 4-methyl-1-(5-propyloxy-3-pyridyl)-piperazine
- 3,5-bis-(N,N'-homopiperazinyl)-pyridine
- 20 5-ethoxy-3-pyridyl-4-ethyl-homopiperazine
- 5-ethoxy-3-pyridyl-4-propyl-homopiperazine
- 5-ethoxy-3-pyridyl-4-(prop-2-en-1-yl)-homopiperazine
- 5-propyl-1,2-epoxy-1-oxy-3-pyridyl-homopiperazine
- 5-phenylacetylenyl-3-pyridyl-homopiperazine
- 25 1-(5-(2-ethyl-1-butoxy)-3-pyridyl)-homopiperazine
- 1-(5-(1-methyl-1-prop-2-en-oxy)-3-pyridyl)-homopiperazine
- 1-(5-(cyclobutylmethoxy)-3-pyridyl)-homopiperazine
- 1-(5-(hex-2-en-oxy)-3-pyridyl)-homopiperazine
- 1-(5-(2-methyl-1-prop-1-en-oxy)-3-pyridyl)-homopiperazine

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or a pharmaceutically acceptable addition salt thereof;

Pharmaceutical acceptable addition salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-

- 5 toxic inorganic and organic acid addition salts such as the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulfonate derived from benzenesulfonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the formate derived from
10 formic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulfonate derived from methane sulphonic acid, the
15 naphthalene-2-sulphonate derived from naphthalene-2-sulphonic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the sulphate derived from sulphuric acid, the tartrate
20 derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulfonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

- 25 Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

The chemical compound of the invention may be provided in solved or unsolved form together with a pharmaceutically acceptable solvents such as water, ethanol and the like. In general, solved forms are considered equivalent to dissolved forms for the purposes of this

30 invention.

Steric isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques.

- 5 One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or
10 camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric

- 15 carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

- 20 Moreover, some of the chemical compounds of the invention contains double bonds and may thus exist in two forms, cis- and trans-forms (Z- and E-form), depending on the arrangement of the substituents around the -C=C- double bond. A chemical compound of the present invention may thus be the cis- or trans-form (Z- and E-form), or it may be a mixture hereof.

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Definition of substituents

Halogen is fluorine, chlorine, bromine or iodine.

- Alkyl means a straight chain or branched chain of one to eight carbon atoms, including but
30 not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl;

Cycloalkyl means cyclic alkyl of three to seven carbon atoms, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;

Alkenyl means a group of from two to eight carbon atoms, including at least one double bond, for example, but not limited to ethenyl, 1- or 2-propenyl, 1-,2- or 3-butenyl, 1-, 2-,3- or 4-pentenyl, 1-,2-,3-,4- or 5-hexenyl, 1-,2-,3-,4-,5-,6-heptenyl, 1-,2-,3-,4-,5-,6-,7-octenyl.

- 5 Alkynyl means a group of from two to eight carbon atoms, including at least one triple bond, for example, but not limited to ethynyl, 1- or 2- propynyl, 1-,2-, or 3 -,3-or butynyl, 1-,2-,3- or 4-pentynyl, 1-,2-,3-,4- or 5-hexynyl, 1-,2-,3-,4-,5- or 6-heptynyl, 1-,2-,3-,4-,5-,6- or 7-octynyl

Thioalkyl is -S-alkyl, wherein alkyl is as defined above;

- 10 Thioalkenyl is -S-alkenyl, wherein alkenyl is as defined above;

Thioalkynyl is -S-alkynyl, wherein alkynyl is as defined above;

Selenoalkyl is -Se-alkyl, wherein alkyl is as defined above;

Selenoalkenyl is -Se-alkenyl, wherein alkenyl is as defined above;

Selenoalkynyl is -Se-alkynyl, wherein alkynyl is as defined above;

15

Cycloalkylalkyl means cycloalkyl as above and alkyl as above, meaning for example, cyclopropylmethyl.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

20

Cycloalkoxy is O-cycloalkyl, wherein cycloalkyl is as defined above.

Alkenoxy is O-alkenyl wherein alkenyl is as defined above.

- 25 Alkynoxy is O-alkynyl, wherein alkynyl is as defined above;

Amino is NH_2 or NH-alkyl or N-(alkyl)₂, wherein alkyl is as defined above.

- 30 A monocyclic 5- 6--membered heterocyclic group includes, for example, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-4-yl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-

pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl and 3-pyrazinyl and 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl

HET represents a non-aromatic heterocycle containing at least one heteroatom such as
5 aziridine, azitidine, azacyclobutene, pyrrolidine, 2,3-dihydro-pyrrole, 3,4-dihydro-pyrrole, piperidine, piperazine, 2,3-dihydropyridine, 3,4-dihydropyridine, 4,5-dihydropyridine, 5,6-dihydropyridine, tetrahydropyridine, homopiperazine, azacyclooctane, diazacyclooctane, homopiperidine, morpholine;

- 10 A bicyclic heterocyclic group composed of a 5 to 6 membered monocyclic heterocyclic group and a fused benzene ring means a monocyclic 5 to 6 membered heterocyclic group as above which is fused to a benzene ring including, for example,
2-, 3-, 4-, 5-, 6-, 7-benzofuranyl, 1-, 2-, 4-, 5- benzimidazolyl, 2-, 3-, 4-, 5-, 6-, 7-indolyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinoliny and 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinoliny.

15

Aryl is an aromatic hydrocarbon, such as phenyl and naphthyl.

Aralkyl means alkyl as above and aryl as above, meaning for example benzyl, phenethyl.

- 20 Isotopes means one or more atom in the compound is substituted with an isotope of the naturally occurring atoms and includes though not limited to deuterium, tritium, ^{13}C , ^{14}C , ^{131}I , ^{125}I , ^{123}I , ^{18}F ;

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms
25 with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

It will be appreciated by those skilled in the art that the compounds of the present invention
30 may contain several chiral centers and that such compounds exist in the form of isomers (i.e. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods, for example, by
35 separation of diastereomeric salts thereof with an optically active acid, and liberating the

optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallization of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the compounds of the present invention with an optically active chloroformate or the like.

Additional methods for the resolution of optical isomers, known to those skilled in the art may be used, and will be apparent to the average worker skilled in the art. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

The compounds of the invention may be prepared by any conventional method useful for the preparation of analogous compounds and as described in the examples below.

Starting materials for the processes described in the present patent application are known or can be prepared by known processes from commercially available materials.

A compound of the invention can be converted to another compound of the invention using conventional methods.

The products of the reactions described herein are isolated by conventional means such as extraction, crystallization, distillation, chromatography, and the like.

Biology

Nicotinic ACh receptors in the brain are pentameric structures composed of subunits distinct from those found in skeletal muscles. The existence of seven α -subunits ($\alpha 2$ - $\alpha 7$, $\alpha 9$) and three β -subunits ($\beta 2$ - $\beta 4$) in the mammalian brain has been described.

The predominant subtype with high affinity for nicotine is comprised of α_4 and β_2 subunits.

The affinity of compounds of the invention for nicotinic ACh receptors have been investigated

- 5 In three test for *in vitro* inhibition of ^3H -epibatidin binding, ^3H - α -bungarotoxin binding and ^3H -cytisine binding as described below:

***In vitro* inhibition of ^3H -cytisine binding**

- 10 The predominant subtype with high affinity for nicotine is comprised of α_4 and β_2 subunits. nAChRs of the latter type can selectively be labelled by the nicotine agonist ^3H -cytisine.

Tissue Preparation: Preparations are performed at 0-4°C unless otherwise indicated.

Cerebral cortices from male Wistar rats (150-250 g) are homogenized for 20 sec in 15 ml

- 15 Tris, HCl (50 mM, pH 7.4) containing 120 mM NaCl, 5 mM KCl, 1 mM MgCl_2 and 2.5 mM CaCl_2 using an Ultra-Turrax homogenizer. The homogenate is centrifuged at 27,000 x g for 10 min. The supernatant is discarded and the pellet is resuspended in fresh buffer and centrifuged a second time. The final pellet is resuspended in fresh buffer (35 ml per g of original tissue) and used for binding assays.

20

Assay: Aliquots of 500 μl homogenate are added to 25 μl of test solution and 25 μl of ^3H -cytisine (1 nM, final concentration), mixed and incubated for 90 min at 2°C. Non-specific binding is determined using (-)-nicotine (100 μM , final concentration). After incubation the samples are added 5 ml of ice-cold buffer and poured directly onto Whatman GF/C glass

- 25 fibre filters under suction and immediately washed with 2 x 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

***In vitro* inhibition of ^3H - α -bungarotoxin binding Rat brain**

30

α -Bungarotoxin is a peptide isolated from the venom of the Elapidae snake *Bungarus multicinctus* (Mebs et al., Biochem. Biophys. Res. Commun., 44(3), 711 (1971)) and has high affinity for neuronal and neuromuscular nicotinic receptors, where it acts as a potent antagonist. ^3H - α -Bungarotoxin binds to a single site in rat brain with a unique distribution

35 pattern in rat brain (Clarke et al., J. Neurosci. 5, 1307-1315 (1985)).

^3H - α -Bungarotoxin labels nAChR formed by the α_7 subunit isoform found in brain and the α_1 isoform in the neuromuscular junction (Changeaux, Fidia Res. Found. Neurosci. Found. Lect. 4, 21-168 (1990). Functionally, the α_7 homo-oligomer expressed in oocytes has a calcium permeability greater than neuromuscular receptors and, in some instances greater than NMDA channels (Seguela et al., J. Neurosci. 13, 596-604 (1993).

Tissue preparation: Preparations are performed at 0-4°C unless otherwise indicated. Cerebral cortices from male Wistar rats (150-250 g) are homogenized for 10 sec in 15 ml 20 mM Hepes buffer containing 118 mM NaCl, 4.8 mM KCl, 1.2 mM MgSO_4 and 2.5 mM CaCl_2 (pH 7.5) using an Ultra-Turrax homogenizer. The tissue suspension is centrifuged at 27,000 x g for 10 min. The supernatant is discarded and the pellet is washed twice by centrifugation at 27,000 x g for 10 min in 20 ml fresh buffer, and the final pellet is resuspended in fresh buffer containing 0.01% BSA (35 ml per g of original tissue) and used for binding assays.

Assay: Aliquots of 500 μl homogenate are added to 25 μl of test solution and 25 μl of ^3H - α -bungarotoxin (2 nM, final concentration), mixed and incubated for 2 h at 37°C. Non-specific binding is determined using (-)-nicotine (1 mM, final concentration). After incubation the samples are added 5 ml of ice-cold Hepes buffer containing 0.05% PEI and poured directly onto Whatman GF/C glass fibre filters (presoaked in 0.1% PEI for at least 6 h) under suction and immediately washed with 2 x 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

25 *In vitro* inhibition of ^3H -epibatidin binding

Epibatidin is an alkaloid that was first isolated from the skin of the Ecuadoran frog *Epipedobates tricolor* and was found to have very high affinity for neuronal nicotinic receptors, where it acts as a potent agonist. ^3H -epibatidin binds to two sites in rat brain, both of which have pharmacological profiles consistent with neuronal nicotinic receptors and a similar brain regional distribution (Hougling et al., Mol. Pharmacol. 48, 280-287 (1995)).

The high affinity binding site for ^3H -epibatidin is most certainly binding to the $\alpha_4\beta_2$ subtype of nicotinic receptors. The identity of the low affinity site is still unknown; does it represent a second nicotinic receptor or a second site in the same receptor. The inability of α -

bungarotoxin to compete for ^3H -epibatidin binding sites indicates that neither site measured represents the nicotinic receptor composed of α_7 subunits.

Tissue preparation: Preparations are performed at 0-4°C unless otherwise indicated. The

- 5 forebrain (\pm cerebellum) from a male Wistar rat (150-250 g) is homogenized for 10- 20 sec in 20 ml Tris, HCl (50 mM, pH 7.4) using an Ultra-Turrax homogenizer. The tissue suspension is centrifuged at 27,000 x g for 10 min. The supernatant is discarded and the pellet is washed three times by centrifugation at 27,000 x g for 10 min in 20 ml fresh buffer, and the final pellet is resuspended in fresh buffer (400 ml per g of original tissue) and used for binding assays.
- 10 Assay: Aliquots of 2.0 ml homogenate are added to 0.100 ml of test solution and 0.100 ml of ^3H -epibatidin (0.3 nM, final concentration), mixed and incubated for 60 min at room temperature. Non-specific binding is determined using (-)-nicotine (30 μM , final concentration). After incubation the samples are poured directly onto Whatman GF/C glass fibre filters (presoaked in 0.1% PEI for at least 20 min) under suction and immediately washed with 2 x 5
- 15 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

Compound	^3H - cytisine $\text{IC}_{50}(\mu\text{M})$	^3H - epibatidin $\text{IC}_{50}(\mu\text{M})$	^3H - α - bungarotoxin $\text{IC}_{50}(\mu\text{M})$
1-[5-(Butoxy)-3-pyridyl]-1,5-diazacyclooctane fumaric acid salt	0,002	0,003	30,0
1-(5-Methoxy-3-pyridyl)-4-ethyl-piperazine fumaric acid salt	0,46	0,71	30,0
4-Ethyl-1-(5-propyloxy-3-pyridyl)-piperazine fumaric acid salt	0,12	0,38	30,0
1-(5-Ethoxy-3-pyridyl)-4-ethyl-homopiperazine fumaric acid salt	0,061	0,37	>30,0
1-(5-Ethoxy-3-pyridyl)-4-propyl-homopiperazine fumaric acid salt (NS3966	0,26	1,6	85,0
1-(5-Ethoxy-3-pyridyl)-4-(prop-2-en-1-yl-)homopiperazine fumaric acid salt	0,037	0,23	>30,0
1-[5-(Propyl-1,2-epoxy-1-oxy)-3-pyridyl]-	0,023	0,040	58,0

homopiperazine			
1-(5-Phenylacetylenyl-3-pyridyl) homopiperazine fumaric acid salt	0,007	0,005	11,0
1-(5,6-Dichloro-3-pyridyl)-homopiperazine fumaric acid salt	0,004	0,002	<3,0
1-(6-Bromo-5-chloro-3-pyridyl)-homopiperazine fumaric acid salt	0,001	0,002	<3,0
1-(5,6-Dibromo-3-pyridyl)-homopiperazine fumaric acid salt	0,001	0,001	3,0
1-(5-Bromo-6-chloro-3-pyridyl)-homopiperazine fumaric acid salt	<0,030	0,001	<3,0
1-[5-(2-Ethyl-1-butoxy)-3-pyridyl]homopiperazine fumaric acid salt	0,004	0,013	>30,0
1-[5-(1-Methyl-1-prop-2-en-oxy)-3- pyridyl]homopiperazine fumaric acid salt	0,011	0,052	11,0
1-[5-(Cyclobutylmethoxy)-3-pyridyl]homopiperazine fumaric acid salt	0,001	0,004	>30,0
1-[5-(Hex-2-en-oxy)-3-pyridyl]homopiperazine fumaric acid salt	0,006	0,008	47,0
1-[5-(2-Methyl-1-prop-1-en-oxy)-3- pyridyl]homopiperazine fumaric acid salt	0,022	0,020	85,0
1-[5-(N-Butyl-N-methylamino)-3- pyridyl]homopiperazine fumaric acid salt	0,28	0,27	85,0
1-[5-(N-pyrrolidinyl)-3-pyridyl]homopiperazine fumaric acid salt	0,008	0,040	5,0
1-(6-Bromo-3-pyridaziny)-homopiperazine fumaric acid salt	0,020	0,070	1,5

Pharmaceutical Compositions

- 5 While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing ten (10) milligrams of active ingredient or, more broadly, 0.1 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

- 5 In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc,

- 10 sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges
15 are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

- For preparing suppositories, a low melting wax, such as admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein,
20 as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

- Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such
25 carriers as are known in the art to be appropriate.

- Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

30

- The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as
35 suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory

agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

5

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided
10 active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions,
15 suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be
20 formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

25

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

30

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the

case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol

- 5 formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

10

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP).

Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition

- 15 may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal

formulations, the compound will generally have a small particle size for example of the order

- 20 of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

25

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or
30 ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

Method of Treating

The compounds of the present invention are valuable nicotinic ACh receptor modulators and therefore useful for the treatment of a range of ailments involving cholinergic dysfunction as well as a range of disorders responsive to the activity of nicotinic ACh receptor modulators.

- 5 The compounds exert their effect on the nicotine receptor complex in a manner which can be characterised by their agonistic character. As such the compounds of the present invention are ranging from behaving as agonists, partial agonist to antagonists.

The compounds may be used in the treatment, prevention, prophylaxis or alleviation of a disease, disorder or condition of the central or peripheral system as for example:

- 10 neurodegenerative disorders, cognitive or memory dysfunction, Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourettes syndrome, attention deficit hyperactivity disorder, anxiety, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders, eating disorders like anorexia nervosa, bulimia and obesity, narcolepsy, nociception, memory loss, memory
15 dysfunction, AIDS-dementia, senile dementia, peripheral neuropathy, learning deficit, cognition deficit, attention deficit, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, chronic fatigue syndrome, disorders of sleep, pseudodementia, Ganser's syndrome, premenstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, premature ejaculation, erectile difficulty, mutism and
20 trichotillomania.

The compounds of this invention may also be used in the treatment of inflammatory conditions as for example: inflammatory skin conditions like acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, irritable colon, diarrhoea.

25

Also the compounds of the invention may be used in the treatment of diseases associated with smooth muscle contractions as for example: convulsive disorders, angina pectoris, premature labor, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia.

- 30 The compounds of this invention may also be used in the treatment of pain as for example chronic, acute and recurrent pain, postoperative pain, migraine pain or phantom limb pain; The compounds of the present invention may also be used for the assistance in cessation of abuse of chemical substances as for example smoking cessation as well as cessation of use of other nicotine containing products, cessation of use of opioids like heroin, cocaine and
35 morphine and cessation of use of benzodiazepines or alcohol. In the context of the present

invention "treatment" means as well treatment as prevention, prophylaxis and alleviation of withdrawal symptoms and abstinence as well as treatment resulting in a voluntary diminished intake of the addictive substance.

- 5 Suitable dosage range are 0.1-500 milligrams daily, and especially 10-70 milligrams daily, administered once or twice a day, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

10

I.p. means intraperitoneally, which is a well known route of administration.

P.o. means peroral, which is a well known route of administration.

The invention then comprises the following alone or in combination:

15

The use as above wherein the disease to be treated is pain, a disease in the central or peripheral system, a disease caused by smooth muscle contraction, neurodegeneration, inflammation, chemical substance abuse or withdrawal symptoms caused by the cessation of intake of the chemical substance, such as assistance in the cessation of smoking;

20

The use as above wherein a disease in the central or peripheral system is Alzheimer's disease, Parkinson's disease, memory dysfunction or attention deficit hyperactivity disorder.

The method as above wherein pain, a disease in the central or peripheral system, a disease
25 caused by smooth muscle contraction, neurodegeneration, inflammation, chemical substance abuse or withdrawal symptoms caused by the cessation of intake of chemical substances, such as smoking cessation, is treated.

The method as above wherein chemical substance abuse or withdrawal symptoms caused by the cessation of intake of the chemical substance, said chemical substance abuse being
30 smoking or use of other nicotine containing products and withdrawal symptoms caused by cessation of use of nicotine containing products, is treated;

A method as above wherein a disease in the central or peripheral system, said disease being Alzheimer's disease, Parkinson's disease, memory dysfunction or attention deficit hyperactivity disorder, is treated.

35

The following examples will illustrate the invention further, however, they are not to be construed as limiting.

Examples

- 5 **General:** All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulfate is used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

Method A

10

4-Methyl-1-(3-pyridyl)-piperazine fumaric acid salt

- A solution of 1-(3-pyridyl)-piperazine (0.35 g, 2.1 mmol), formic acid (1.0 g, 21.7 mmol), formaldehyde (0.64 g, 37 %) and water (2 ml) was stirred at reflux for 15 h. The mixture was evaporated and sodium hydroxide (30 ml, 1 M) was added and the product was extracted
15 three times with ethyl acetate (15 ml). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 0.21 g, 34 %. Mp 144.5 - 145.9 °C.

1-(5-Pentyloxy-3-pyridyl)-4-methyl-piperazine fumaric acid salt

- 20 Was prepared according to method A. Mp 113.6-115.1 °C.

1-[5-(*trans*-Hex-2-en-1-yloxy-3-pyridyl)]-4-methyl-piperazine fumaric acid salt

Was prepared according to method A. Mp 113.0-114.9 °C.

25

Method B

1-(3-Pyridyl)-piperazine fumaric acid salt

- A solution of 1-(3-pyridyl)-4-*tert*-butoxycarbonylpiperazine (1.3 g, 4.9 mmol), trifluoroacetic acid (11.3 g, 99 mmol) and dichloromethane (50 ml) was stirred for 15 h. The mixture was
30 evaporated. Sodium hydroxide (30 ml, 4 M) was added. The product was extracted three times with dichloromethane (50 ml) and isolated as an oil. Yield 0.72 g, 90 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1), saturated with fumaric acid. Mp 161.7 - 164.8 °C.

Method C**1-(3-Pyridyl)-4- *tert*-butoxycarbonyl-piperazine**

A mixture of 3-bromopyridine (7.8 g, 49.4 mmol), 1-*tert*-butoxycarbonylpiperazine (9.2 g, 49.4 mmol), tetrakis(triphenylphosphine)palladium(0) (286 mg, 0.247 mmol), potassium *tert*-butoxide (11.1 g, 98.8 mmol) and anhydrous toluene (100 ml) was stirred at 80 °C for 0.5 h. Water (100 ml) was added and the mixture was extracted three times with ethyl acetate (75 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as an oil. Yield 1.34 g, 10 %.

10 Method D**1-(5-Ethoxy-3-pyridyl)piperazine fumaric acid salt**

A mixture of 3-chloro-5-ethoxypyridine (6.5 g, 45.8 mmol), piperazine (19.7 g, 229 mmol), potassium *tert*-butoxide (11.2 g, 91.6 mmol) and 1,2-dimethoxyethane (150 ml) was stirred at reflux for 1 h. Aqueous sodium hydroxide (1 M, 100 ml) was added and the mixture was extracted two times with ethyl acetate (150 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 4.6 g, 48 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 160.0 - 161.2 °C.

20 1-[5-(Butoxy)-3-pyridyl]-1,5-diazacyclooctane fumaric acid salt

Was prepared according to method D, from 3-chloro-5-(butoxy)-pyridine, stirred at room temperature for 3 days. Mp 146 - 148 °C.

25 1-(5-Ethoxy-3-pyridyl)-4-ethyl-piperazine fumaric acid salt

A mixture of 1-(5-ethoxy-3-pyridyl)-piperazine (1.4 g, 6.8 mmol), triethylamine (0.69 g, 6.8 mmol), bromoethane (0.88 g, 8.1 mmol) and dimethylformamide (25 ml). Aqueous sodium hydroxide (1 M, 50 ml) was added and the mixture was extracted two times with ethyl acetate (50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 0.75 g, 47 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1), saturated with fumaric acid. Mp 144.8 - 145.9 °C.

1-(5-Methoxy-3-pyridyl)-4-ethyl-piperazine fumaric acid salt

Was prepared according to 1-(5-ethoxy-3-pyridyl)-4-ethyl-piperazine. Mp 147.9 - 148.3 °C.

4-Ethyl-1-(5-propyloxy-3-pyridyl)-piperazine fumaric acid salt

Was prepared according to 1-(5-ethoxy-3-pyridyl)-4-ethyl-piperazine. Mp 128.7 - 130.5 °C.

5

Pyridylhomopiperazines

Method A

4-Methyl-1-(3-pyridyl)-homopiperazine

- 10 A solution of 1-(3-pyridyl)-homopiperazine (0.42 g, 2.4 mmol), formic acid (3.3 g, 71.7 mmol), formaldehyde (2.1 g, 37 %) and water (10 ml) was stirred at reflux for 15 h. The mixture was evaporated and sodium hydroxide (15 ml, 4 M) was added and the product was extracted two times with ethyl acetate (15 ml). The product was obtained as an oil. Yield 0.46 g, 100 %.

15 3,5-Bis-(N,N'-homopiperazinyl)-pyridine fumaric acid salt

Was prepared according to method A from 1-[5-(1-(4-*tert*-butoxycarbonylhomopiperazinyl))-3-pyridyl]homopiperazine. Mp 134 - 136 °C.

4-Benzyl-1-(3-Pyridyl)-homopiperazine fumaric acid salt

- 20 1-(3-Pyridyl)-homopiperazine (0.54 g, 3.0 mmol), potassium carbonate (0.42 g, 3.0 mmol), benzylbromide (0.56 g, 3.3 mmol) in dimethylformamide (40 ml) was stirred at 80 °C for one hour. Water (100 ml) was added and the mixture was extracted twice with ethyl acetate (25 ml). Yield 0.39 g, 49 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1), saturated with fumaric acid. Mp 148.4 - 149.0 °C.

25

1-(5-Ethoxy-3-pyridyl)-4-ethyl-homopiperazine fumaric acid salt

Was prepared according to 4-benzyl-1-(3-pyridyl)-homopiperazine. Mp 130.9 - 133.1 °C.

1-(5-Ethoxy-3-pyridyl)-4-propyl-homopiperazine fumaric acid salt

- 30 Was prepared according to 4-benzyl-1-(3-pyridyl)-homopiperazine. Mp 96.5 - 97.5 °C.

1-(5-Ethoxy-3-pyridyl)-4-(prop-2-en-1-yl)-homopiperazine fumaric acid salt

Was prepared according to 4-benzyl-1-(3-pyridyl)-homopiperazine at room temperature. Mp 119.2 - 124.1 °C.

Method B**5 1-(3-Pyridyl)-homopiperazine fumaric acid salt**

A solution of 1-(3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (0.91 g, 3.3 mmol), trifluoroacetic acid (7.5 g, 66 mmol) and dichloromethane (30 ml) was stirred for 15 h. The mixture was evaporated. Sodium hydroxide (30 ml, 4 M) was added. The product was extracted two times with dichloromethane (30 ml) and isolated as an oil. Yield 0.50 g, 85 %.

- 10 The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 172.1 - 172.9 °C.

1-[5-(Propyl-1,2-epoxy-1-oxy)-3-pyridyl]-homopiperazine

Was prepared according to method B. Mp 135.2 - 139.0 °C.

15

1-(5-Phenylacetylenyl-3-pyridyl) homopiperazine fumaric acid salt

Was prepared according to method B. Mp 155.2 - 157.8 °C.

1-(5,6-Dichloro-3-pyridyl)-homopiperazine fumaric acid salt

- 20 Was prepared according to method B. Mp 172.2 - 173.4 °C.

1-(6-Bromo-5-chloro-3-pyridyl)-homopiperazine fumaric acid salt

Was prepared according to method B. Mp 213 - 216 °C.

25 1-(5,6-Dibromo-3-pyridyl)-homopiperazine fumaric acid salt

Was prepared according to method B. Mp 192.1 - 193.2 °C.

1-(5-Bromo-6-chloro-3-pyridyl)-homopiperazine fumaric acid salt

Was prepared according to method B. Mp 188.2 - 189.2 °C.

30

Method C**1-(3-Pyridyl)-4-*tert*-butoxycarbonylhomopiperazine**

A mixture of 3-bromopyridine (3.95 g, 25.0 mmol), 1-*tert*-butoxycarbonylhomopiperazine (5.0 g, 25.0 mmol), tetrakis(triphenylphosphine)palladium(0) (145 mg, 0.125 mmol), potassium

tert-butoxide (6.1 g, 50.0 mmol) and anhydrous toluene (75 ml) was stirred at 80 °C for 4 h. Water (100 ml) was added and the mixture was extracted three times with ethyl acetate (50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as an oil. Yield 0.92 g, 13 %.

5

Method D

1-(5-Methoxy-3-pyridyl)-homopiperazine fumaric acid salt

A mixture of 3-bromo-5-methoxypyridine (5.6 g, 30.0 mmol), homopiperazine (15.0 g, 150 mmol), tetrakis(triphenylphosphine)palladium(0) (173 mg, 0.15 mmol), potassium-*tert*-butoxide (6.7 g, 60 mmol) and anhydrous toluene (150 ml) was stirred at 80 °C for 4 h. Water (100 ml) was added and the mixture was extracted seven times with ethyl acetate (150 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 3.5 g, 56 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 161 - 162 °C.

15

Method E

1-[(5-Methoxy-methoxy)-3-pyridyl]-homopiperazine fumaric acid salt

A mixture of 3-chloro-5-methoxymethoxypyridine (10.0 g, 57.6 mmol), homopiperazine (28.8 g, 288 mmol), 1.3-bis(diphenylphosphino)propanepalladiumdichloride (170 mg, 0.29 mmol),
20 potassium *tert*-butoxide (12.9 g, 115 mmol) and 1,2-dimethoxyethane (100 ml) was stirred at reflux for 3 h. Sodium hydroxide (1 M, 100 ml) was added and the mixture was extracted two times with ethyl acetate (150 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 9.7 g, 71 %.
The corresponding salt was obtained by addition of a diethyl ether and methanol mixture
25 (9:1) saturated with fumaric acid. Mp 129.5 - 131 °C.

Method F

1-(5-(1-Pyrrolyl)-3-pyridyl)-homopiperazine fumaric acid salt

30 A mixture of 3-chloro-5-(1-pyrrolyl)-pyridine (6.3 g, 35.3 mmol), homopiperazine (7.06 g, 70.5 mmol), potassium *tert*-butoxide (7.91 g, 70.5 mmol) and 1,2-dimethoxyethane (100 ml) was stirred at reflux for 3 h. Sodium hydroxide (1 M, 120 ml) was added and the mixture was extracted three times with ethyl acetate (100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 3.45

g, 40 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 174 - 175 °C.

1-[5-(2-Ethyl-1-butoxy)-3-pyridyl]homopiperazine fumaric acid salt

5 Was prepared according to method F. Mp 113.7 -115.9 °C.

1-[5-(1-Methyl-1-prop-2-en-oxy)-3-pyridyl]homopiperazine fumaric acid salt

Was prepared according to method F. Mp 129.5 -133.6 °C.

10 **1-[5-(Cyclobutylmethoxy)-3-pyridyl]homopiperazine fumaric acid salt**

Was prepared according to method F. Mp 158.9 -159.9 °C.

1-[5-(Hex-2-en-oxy)-3-pyridyl]homopiperazine fumaric acid salt

Was prepared according to method F. Mp 126.8 -130.2 °C.

15

1-[5-(2-Methyl-1-prop-1-en-oxy)-3-pyridyl]homopiperazine fumaric acid salt

Was prepared according to method F, with reflux for 3 days to ensure complete isomerisation of the double bond from 1-[5-(1-Methyl-1-prop-2-en-oxy)-3-pyridyl]homopiperazine. Mp 114.4 -116.0 °C.

20

1-[5-(N-Butyl-N-methylamino)-3-pyridyl]homopiperazine fumaric acid salt

Was prepared according to method F. Mp 140.5 -141.8 °C.

25 **1-[5-(N-pyrrolidiny)-3-pyridyl]homopiperazine fumaric acid salt**

Was prepared according to method F. Mp 141.5 -143.0 °C.

1-[5-(1-(4-*tert*-butoxycarbonyl)homopiperazinyl))-3-pyridyl]homopiperazine fumaric acid salt

30 Was prepared according to method F from 1-(5-chloro-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine. Mp 184 -186 °C.

1,4-Bis [5-ethoxy-3-pyridyl] homopiperazine fumaric acid salt

Was prepared according to method F as the minor product. Mp 155-156°C.

1,4-Bis [5-(1-propyl-1-en-oxy)-3-pyridyl] homopiperazine fumaric acid salt

5 Was prepared according to method F as the minor product. Mp 156-158 °C.

1-(5-Bromo-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine

A mixture of 1-(5-bromo-3-pyridyl)-homopiperazine (19.0 g, 74.2 mmol), and di-*tert*-butyl dicarbonat (16.2 g, 74.2 mmol), triethylamine (7.5 g, 74.2 mmol) and dichloromethane (200
10 ml) was stirred at roomtemperature for 1 h. The crude mixture was purified by chromatography on silica gel using ethyl acetate : petroleum (1 : 1) as solvent. Yield 16.6 g, 55 %.

1-(5-Chloro-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine

15 Was prepared from 1-(5-Chloro-3-pyridyl)-homopiperazine according to 1-(5-Bromo-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine.

1-(5-Phenylacetylenyl-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine

20 A mixture of 1-(5-bromo-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (3.5 g, 9.8 mmol), phenylacetylene (2.0 g, 19.6 mmol), tetrakis(triphenylphosphine)palladium(0) (100 mg, 0.086 mmol), diethylamine (1.4 g, 19.6 mmol) and tetrahydrofuran (50 ml) was refluxed for 5 h. Aqueous sodium hydroxide (75 ml, 1M) was added. The mixture was extracted twice with ethyl acetate. The mixture was purified by chromatography on silica gel using ethyl acetate :
25 petroleum (1 : 1) as solvent. Yield 0.54 g, 7.3 %.

1-(5,6-Dichloro-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine

A mixture of 1-(5-chloro-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (1.56, 5.0 mmol), 1,3-dichloro-5,5-dimethylhydantoin (0.985 g, 5.0 mmol) and dichloromethane (50 ml) was
30 stirred for 180 min. The crude mixture was evaporated and purified by chromatography on silica gel using ethyl acetate : petroleum (3 : 1) as solvent. Yield 0.46 g, 27 %.

1-(6-Bromo-5-chloro-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine

A mixture of 1-(5-chloro-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (2.34 g, 7.5 mmol), N-bromosuccinimide (1.34 g, 7.5 mmol) and acetonitrile (75 ml) was stirred for 60 min. The crude mixture was evaporated and purified by chromatography on silica gel using ethyl acetate : petroleum (2 : 1) as solvent. Yield 2.5 g, 85 %.

5

1-(5,6-Dibromo-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine

A mixture of 1-(5-bromo-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (2.68 g, 7.5 mmol), N-bromosuccinimide (1.34 g, 7.5 mmol) and acetonitrile (75 ml) was stirred for 30 min. The crude mixture was evaporated and purified by chromatography on silica gel using ethyl acetate : petroleum (2 : 1) as solvent. Yield 3.0 g, 92 %.

10

1-(5-Bromo-6-chloro-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine

A mixture of 1-(5-bromo-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (2.68 g, 7.5 mmol), 1,3-dichloro-5,5-dimethylhydantoin (0.89 g, 4.5 mmol) and acetonitrile (75 ml) was stirred for 45 min. The crude mixture was evaporated and purified by chromatography on silica gel using ethyl acetate : petroleum (2 : 1) as solvent. Yield 0.80 g, 51 %.

15

Method G

20 1-(6-Chloro-3-pyridazinyl)-homopiperazine fumaric acid salt

A mixture of 2,6-dichloropyridazine (5.0 g, 33.5 mmol), homopiperazine (3.36g, 33.5 mmol) and 50 ml of toluene was stirred at reflux for 0.5h. Sodium hydroxide (50 ml, 1M) was added and the mixture was extracted three times with ethyl acetate (100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 2.2g, 31%. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 165-166 °C.

25

1-(6-Bromo-3-pyridazinyl)-1,5-diazacyclooctane fumaric acid salt

Was prepared according to method G, using dioxane at reflux. 3,6-Dibromopyridazine (P. Coad, R. A. Coad, S. Clough, J. Hyepock, R. Salisbury and C Wilkins, J. Org. Chem. 1963, 28, 218-221) and 1,5-diazacyclooctane was used as starting material Mp 164.5-166.5 °C.

30

1-(6-Bromo-3-pyridazinyl)-homopiperazine fumaric acid salt

Was prepared according to method G. Mp 169-171 °C.

Method H**1-(3-Pyridazinyl)-homopiperazine**

- 5 A mixture of 1-(3-chloro-6-pyridazinyl)-homopiperazine (5.56 g, 26.1 mmol), palladium on carbon (2.1 g, 10 %) and ethanol (150 ml) was stirred under hydrogen overnight. The crude product was filtered through celite and evaporated. Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 2.78 g, 60 %, 185.0 - 186.9 °C.

10

1-[5-(Propyl-1-en-oxy)-3-pyridyl]-4-*tert*-butoxycarbonyl-homopiperazine

- A mixture of 1-[5-(propyl-1-en-oxy)-3-pyridyl]-homopiperazine (5.0 g, 21.7 mmol), *tert*-butoxycarbonyl anhydride (5.7 g, 26.0 mmol), triethylamine (4.4 g, 43.4 mmol) and dichloromethane (100 ml) was stirred 1 h at room temperature. The organic phase was
15 washed twice with an aqueous mixture of sodium hydroxide (50 ml, 1 M). Chromatography on silica gel with dichloromethane and methanol (19 : 1) gave the title compound as free base as an oil. Yield 5.9 g, 82 %.

1-[5-(Propyl-1,2-epoxy-1-oxy)-3-pyridyl]-4-*tert*-butoxycarbonyl-homopiperazine

- 20 A mixture of 1-[5-(propyl-1-en-oxy)-3-pyridyl]-4-*tert*-butoxycarbonyl-homopiperazine (2.0 g, 5.7 mmol), *m*-chloro-perbenzoic acid (1.3 g, 7.4 mmol) and chloroform (75 ml) was stirred at roomtemperature for 2 h. Sodium hydroxide (150 ml, 1 M) was added, the aqueous phase was discarded and the organic phase was washed with sodium hydroxide (100 ml, 1 M). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1)
25 gave the title compound as free base. Yield 0.89 g, 45 %.

30